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Computer Modeling of Epilepsy

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This chapter reviews current computational models and proposes future directions for computer modeling in the field of epilepsy. We consider the potential therapeutic applications of modeling in the both the treatment and prevention of epilepsy. Additionally, we discuss the benefits of computer modeling for research. The models discussed include single cells with mutated ion channels, mean-field network and detailed network models. We conclude by suggesting some excellent resources for those interested in learning more about computer modeling in neuroscience and epilepsy.

There are 50 million people worldwide already afflicted with epilepsy and for roughly 15 million of them existing epilepsy treatments are not sufficient.[1] Such stark facts spur clinicians and researchers to consider dramatically different approaches to treatment, such as an implantable device that could characterize electrical activity in real time, immediately detect when the brain reaches a pre-ictal state and apply a counteracting current waveform, averting the seizure before it starts (see next section),[2] or an individualized, detailed model of the patient's brain – complete with patient-specific details such as genetic mutations or head trauma – to which doctors could administer virtual drugs to determine the best treatment regimen for that person. Such a tool would complement existing therapies by reducing the likelihood of patients being subjected to treatments for which they are unresponsive.

Notably, both the implantable device and the individualized brain model use computer modeling. The device employs computer modeling in its development and in the algorithms it uses to detect the seizure and formulate an appropriate response, whereas the individualized model would use an interactive, large-scale, biologically realistic computational model.

And then there are the 2.4 million people worldwide who will develop epilepsy over the next year due to a variety of causes.[1] Ideally, we could prevent epileptogenesis in these people entirely, and computer modeling can help us achieve this goal. For example, in people who have experienced head trauma, an ideal therapy might be a drug that could be administered to prevent the ensuing of epileptogenic alterations without disrupting the brain further. Computational models could help us determine which of the alterations are most clinically significant

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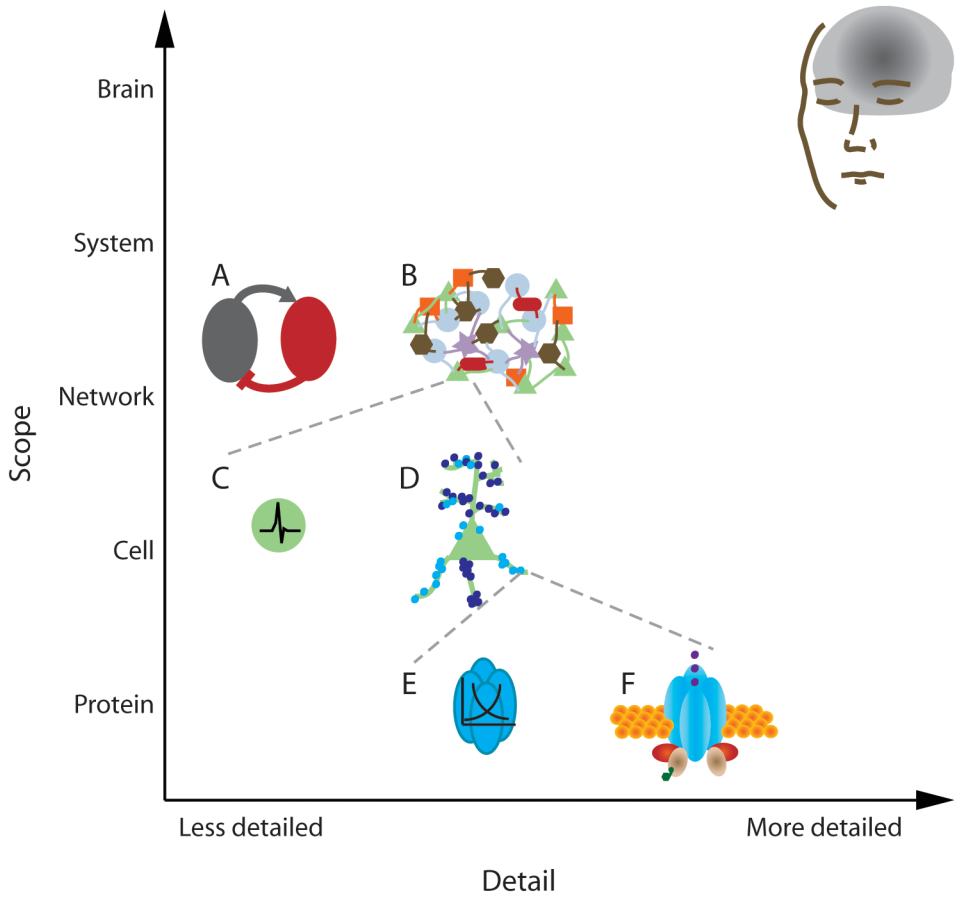

Figure 1. Functional computational models can be partially organized by their scope and detail. The icons above represent a few possible modeling approaches mentioned in this chapter. **A:** Macroscopic, mean-field network models, which usually incorporate at least an excitatory and an inhibitory neuronal population. **B:** Detailed network models, which include individual cells modeled at variable amounts of detail. Note that both A and B can describe networks or even systems that can perform higher-level functions. **C – D:** Model cells at variable levels of detail, from integrate-and-fire models (C) to cells with simple morphology and mechanisms representing ion channels, receptors, and gap junctions (D). **E - F:** Ion channels and other subcellular mechanisms can also be represented at variable levels of detail, from their conductances in each state (E) to detailed protein structures that capture conformational changes and binding sites (F).

and also help characterize the therapeutic and side effects of any proposed treatment. In patients with gene mutations, a method to induce expression of a "therapeutic" ion channel could counteract the epileptic effects of a mutated ion channel.[3] Again, an individualized computational model of the brain could help by predicting the likelihood of epileptogenesis (and therefore the need for treatment) in someone exposed to a particular environmental or genetic factor.

Such ideas may sound impractical, even outlandish given the current state of epilepsy therapy. However, work has already begun on projects similar to the ideas above. For example, the Blue Brain Project has created a detailed, 10,000 neuron model of a rat neocortical column[4] and aims to build a detailed, biologically realistic model of the human brain.[5] Also impressive, there are several implantable devices undergoing clinical trials, some of which use algorithms that can be individually tuned for each subject by their doctor to detect and respond to seizures.[2]

Clearly, there is a role for computer modeling in the development and operation of epilepsy therapies. Not only can it be applied directly to therapies, like the examples above, but it can also guide researchers in choosing and designing experiments and can provide a framework for organizing experimental results. In fact, computational models have already advanced our understanding of disorders such as schizophrenia,[6] Parkinson's disease,[7]

stroke,[8] and, of course, epilepsy.[9] Within the field of computational epilepsy modeling, approaches include single-cell[10–12] models (simple or detailed) and network models ranging from mean-field[13–14] to large-scale, detailed models[15–19] (Figure 1).

This range of approaches is not surprising, given that epilepsy is a dynamical disorder that can be characterized at multiple levels of detail.[20] Though there exists a wealth of data at each of these levels, the challenge of drawing connections across levels stands in the way of developing greater understanding and new treatments for the disorder. For example, it is difficult to understand how high level dynamics such as aggregate electrical activity during a seizure could be predicted from low level structural and functional factors like altered connectivity between cells or mutated ion channels. Furthermore, the many causes of epilepsy and its variable manifestations limit our ability to apply knowledge about one epilepsy model to other models. The challenges of integrating experimental research about epilepsy through multiple levels of detail and across multiple subcategories of the disorder can be addressed with computer modeling.

While a thorough survey of modeling techniques in the epilepsy field requires an entire book,[9] much can be learned from a tour of recently developed models. Here, we first discuss computer modeling to benefit patients who already have epilepsy and those at risk for developing epilepsy. Then we illustrate how computer modeling can complement experimental research. After the reader has been introduced to several models, we explicitly describe the various approaches one may take for computer modeling of epilepsy. We conclude by assessing the future of computer modeling in epilepsy and suggest resources available to those interested in using computers to model epilepsy.

COMPUTER MODELING TO PREVENT SEIZURES

Computational modeling is not just useful for clinical applications indirectly via research; it is already directly applicable to clinical practice. Aside from the well-known application of computer modeling to the discovery and development of pharmaceutical agents,[21–22] it has also been instrumental in designing therapies to prevent or reduce seizures, some of which have already been successfully used in human patients. For the purpose of this chapter, such therapies can be broadly classified into dynamic, which only exert their effects in response to seizures, and static, which exert their effects continuously (or continually, in some cases).

Dynamic Therapies

There have been promising developments in devices capable of online analysis of epileptic patients, for the detection of and response to seizures. At least one device, the RNS™ device designed by NeuroPace, has shown a significant reduction in seizure frequency during clinical trials, with an acceptable level of side effects.[2] An application for premarket approval (PMA) for the RNS™ device was recently submitted to the FDA.[23] Though the seizure detection and response algorithm used in the NeuroPace RNS™ device is proprietary, we can review other computational models to highlight some of the computational issues inherent in seizure detection and response.

Detection of seizures requires a reliable method of characterizing seizure and even pre-seizure activity, one that is robust enough to detect each seizure that occurs, despite known variability in individual seizure dynamics. A variety of neural properties have been proposed as suitable for monitoring to detect seizures, including EEG traces[24] and localized glutamate transmission.[25] One such method of characterization is matching pursuit, in which a signal (such as an EEG) is broken down into "atoms," smaller and simpler signal elements.[26] Using this analysis, researchers were able to show considerable similarity among onsets of seizures originating from the same foci in the same patient.[26]

Once a seizure has been detected, there is a variety of approaches to correcting the abnormal activity. In one approach, Lopour et al. (2010) produced a mean-field model that showed how a control system could analyze

the electrode signals from a seizing patient and apply a charge balanced potential to nearby electrodes to terminate the seizure activity.[14] Using a charge balanced correction signal is thought to be less harmful to cortical tissue and is an important step in the eventual goal of using such a controller therapeutically.[14]

With online detection of seizures, much emphasis is placed on how quickly the seizure can be detected; the earlier the stereotyped seizure pattern can be recognized, the more useful such information becomes. Ideally, the events leading to the clinical onset of the seizure could also be characterized well enough to predict the onset of the seizure within a clinically meaningful time window. Seizure prediction cannot be covered in sufficient detail here, but other publications provide insight and discuss the controversies associated with computational modeling for prediction.[27–28]

Even if seizure dynamics could be characterized well enough that detection theoretically could be reliably performed early in the seizure, analysis speed is a challenge. With the Lopour et al. model (2010), we note that the model required five minutes of computation time to analyze seizure dynamics and then compute and deliver charge-balanced correction signal to end the seizure.[14] However, most seizures self-terminate well within five minutes of onset.[29] For such an approach to be helpful, the detection and analysis should finish in just a few seconds, a speed increase of two orders of magnitude. The speed could be shortened by running the analysis at a lower resolution,[14] and more computational resources could be devoted to the task, but some technical innovation will be required for this algorithm to be incorporated in a portable seizure detection device.

Even with a therapeutic device in the FDA approval process, novel approaches to seizure detection and intervention are still relevant. Not all patients respond to the RNS™ device[30] and for those that do, the therapeutic effects are not immediate. Tuning these devices to properly detect seizures currently takes many months, even for patients with relatively frequent seizures (i.e. at least three times a month).[31] For people with less frequent seizures, it is possible that the detection tuning process could take over a year.

Because seizure dynamics vary so widely among patients, it seems that a calibration period will be unavoidable for any detection device. However, as the field of seizure detection advances, calibrating the detection algorithm will likely require fewer seizures and fewer hours of physicians' time. Ideally, devices would be able to calibrate themselves. Current devices are already monitoring the patients' response continuously, even when the patient is receiving the therapeutic correction signal they produce in response to a seizure. As we develop a better understanding of seizure dynamics, that knowledge can be translated into intelligent devices, capable of analyzing and correcting their own performance.

Static Therapies

In contrast to devices that detect and respond to seizures, there are also devices that deliver scheduled pulses, i.e., their activity is defined by a preset pattern (periodic pacing), independently of when the patient seizes. Such devices have also shown promising reduction in seizure frequency and do not require an extended calibration period as they do not need to detect seizures.[2]

Other therapies that exert their effects independently of the patient's state include pharmacological treatments.[21–22] These agents affect subcellular mechanisms, such as ion channels, transporters, pumps, and receptors. Computational models that incorporate these subcellular mechanisms can help identify therapeutic targets and also show how their modulation may influence dynamics at the cellular and network levels.

Here, we will introduce a computational model used by Dyhrfjeld-Johnsen *et al.* (2008) to illustrate the effect of a channelopathy on cellular excitability. Channelopathies - pathological changes in the expression or function of ion channels - are of great interest in the field of epilepsy because they have been linked to both inherited and acquired epilepsies. For those inherited epilepsies whose mutations have been discovered, the mutations have been predominantly channelopathies.[32]

One common channelopathy occurring in epileptic animal models affects the hyperpolarization-activated, cyclic nucleotide-gated (HCN) channel responsible for an inward, mixed-cation current (I_h). Most experimental paradigms report that seizures reduce I_h a reduction thought to increase hyperexcitability[33] because it would lessen the shunting effect associated with I_h. However, in an experimental febrile seizure model, the hyperexcitable dendrites of CA1 pyramidal cells show a marked increase in I_h.[38] Computer modeling provided an explanation for these seemingly contradictory results.

Using a computational model, Dyhrfjeld-Johnsen *et al.* (2008) altered the h-current and examined the effects on the excitability of three detailed pyramidal cell models (Figure 2).[38] The models indicated that an increased I_h can contribute to hyperexcitability (Figure 2A). Analysis of the mechanism by which I_h enhanced excitability showed that the upregulated I_h depolarized the dendritic resting membrane potential, shifting it closer to threshold. When cells with increased I_h were held at the control resting membrane potential, no increase in excitability was observed (Figure 2B). These results highlight the complex relationship between I_h and neuronal excitability; perhaps functional effects cannot be predicted by looking at only the direction of changes in I_h.

Knowing that the hyperexcitability seen in increased I_h is related to the more positive resting membrane potential, we can then propose possible therapeutic interventions. For example, a pharmacological agent that can counteract the more depolarized membrane potential[38] with minimal disturbance to physiological functions, perhaps mediated by the M-current,[38–40] should be sufficient to reduce the I_h-associated network hyperexcitability seen in the above-mentioned febrile seizure model.[38]

COMPUTER MODELING TO PREVENT EPILEPTOGENESIS

Understanding how the healthy brain becomes capable of seizing requires knowledge of the detailed changes associated with epileptogenesis. These alterations include cell loss, changes in network connectivity, mutated ion channels, and altered gene expression profiles. Quite often, multiple changes occur together, obscuring each factor's contribution to the seizure-prone brain. In this scenario, untangling the role of each factor may be far easier in computational models than experimental ones.

Head trauma is one model of epilepsy in which multiple changes are known to occur. These alterations affect, among other brain regions, the dentate gyrus, an area of the hippocampal formation sometimes thought to gate network activity in the healthy brain. Epileptogenic changes seen in the dentate gyrus after head trauma include mossy fiber sprouting and hilar cell loss. Mossy fiber sprouting, i.e., the development of new axonal branches by granule cells, accounts for recurrent excitation among granule cells, consequent to the establishment of reciprocal synaptic contacts that are not normally present in the healthy dentate gyrus. Hilar cell loss does not only affect inhibitory interneurons, but it also reduces the number of excitatory mossy cells. The effect of reducing the number of excitatory mossy cell synapses onto the granule cells is not well understood.

It is quite challenging to separate these alterations in experimental models of epilepsy, but computer modeling provides a flexible way to study the changes in isolation. Santhakumar *et al.* (2005), Dyhrfjeld-Johnsen *et al.* (2007), and Morgan and Soltesz (2008) studied, in progressively more detail, the effects of structural changes in the dentate circuitry on hyperexcitability.[17–19] The first of these studies played a major role in demonstrating the promise of large-scale, data-driven models in epilepsy research as it detailed the construction of the dentate gyrus model, containing four biophysically realistic cell types, each connected via realistic synapses using connection probabilities derived from *in vivo* and *in vitro* experiments. Using the 500-cell model that was thus constructed, Santhakumar *et al.* (2005) were able to show that structural changes alone can predispose the dentate network to hyperexcitability.[19]

Dyhrfjeld-Johnsen *et al.* (2007) expanded the functional model of Santhakumar *et al.* (2005) to over 50,000 cells, a scale of 1:20 compared to the full-size rat dentate gyrus. Their experiments also used a complete 1:1 scale structural model of the dentate gyrus to determine the graph-theoretical characteristics of the dentate network.

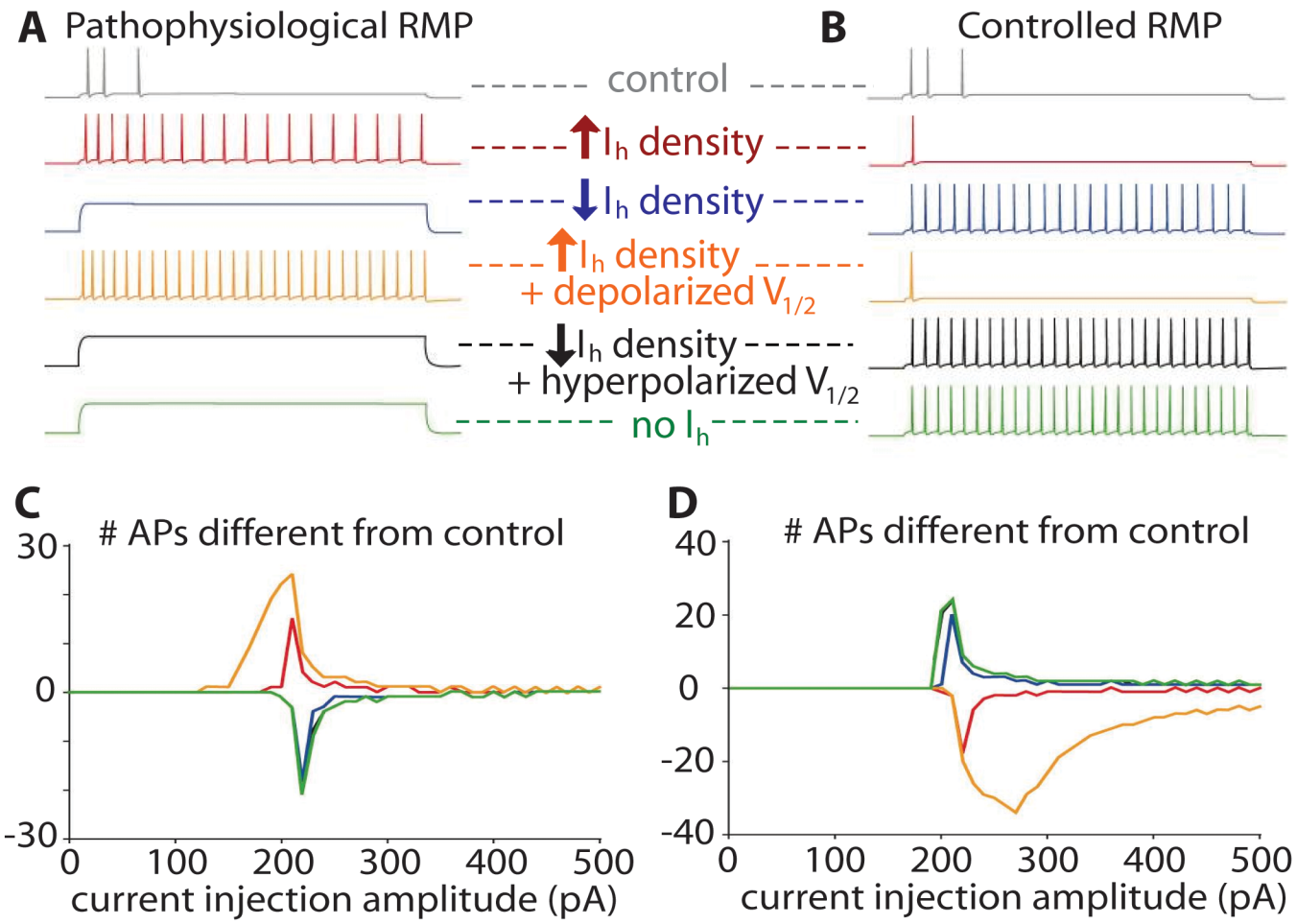

Figure 2. Altered h-current changes neuronal excitability. Both the modified control CA1 pyramidal neuron model[38, 68] and models with altered I_h are subjected to a 1000 ms depolarizing current injection, with the membrane potential allowed to vary from control resting membrane potential (left column) or clamped at control resting membrane potential (right column). **A, B:** Example traces of simulated neuronal behaviors in response to depolarizing current injection (+210 pA), in the cases of pathologically depolarized (A) and controlled (B) resting membrane potential (RMP). **C, D:** For each amplitude of current injection, the activity of the models with altered I_h is contrasted with that of control models by comparing the number of action potentials fired. A positive difference means the pathophysiological model has become more excitable than control; a negative difference indicates the pathophysiological model is less excitable. The resting membrane potential of the pathophysiological model is either set to the pathophysiological, depolarized resting potential (C) or the controlled resting potential (D). Figure adapted from Dyhrfjeld-Johnsen et al. (2009).[69]

The results of the structural model showed that the dentate gyrus is a small-world network. In a small-world network, cells make many connections to their close neighbors, yet the number of cells along a path from a given cell to any distant cell remains quite small due to the presence of a few long distance connections. By combining the structural model results with those of the functional model at varying levels of dentate injury, Dyhrfjeld-Johnsen *et al.* (2007) showed that head injury causes substantial alterations to the small-world structure of the dentate gyrus, resulting in a hyperexcitability profile closely correlated with structural alterations.[17]

Because the specific pattern of new granule cell connections that occurs with mossy fiber sprouting is not known, Morgan and Soltesz (2008) studied the pathological alterations in the dentate gyrus circuitry in even more detail.[18] They questioned whether the hyperexcitability of the sprouted network depends on the specific pattern of new connections.[18] To answer the question, Morgan and Soltesz compared non-random patterns of connectivity to a control network in which the granule cells were connected together randomly (Figure 4A). In each case, the model had the same number of connections among granule cells, but the connections were distributed differently among the cells.

They found that simply rewiring the granule cell network in certain ways could markedly increase excitability (Figure 5). In particular, if the connections were redistributed so that most granule cells had few granule cell connections, but some rare granule cells ("hubs") had many connections (Figure 4B), network activity increased greatly. These highly connected cells made the dentate network significantly more excitable without changing the total excitatory drive of the network, demonstrating the potential importance of hub cells in seizures (compare Figure 5A and 5B). Experimental work has supported the presence of hub cells in the dentate gyrus after injury, thus beginning to validate the model's prediction and pointing to the importance of understanding the microcircuit connectivity in seizure-prone networks.[41] This work suggests that therapeutic efforts to prevent mossy fiber sprouting could reduce epileptogenesis in people who have experienced head trauma.

Epileptogenic changes are not limited to neurons and their connections. Glia dysfunction has been implicated in epileptogenesis, and therefore deserves consideration as a possible therapeutic target.[42–44] Its significance arises especially because of the glial role in regulating the concentration of extracellular potassium, and because of the ability of glial cells to interfere with inhibition,[45] to release ATP,[39] and to affect glutamate concentration at nearby synapses.[11, 44, 46] Cressman et al. (2009) investigated the role of ion concentrations and glia in epileptic networks using a model of a single cell[11] and a network.[44]

In this work, they first examined the effects of intracellular and extracellular ion concentrations on neuronal excitability and seizure frequency with a mathematical model of a neuron and its extracellular space, including the glia surrounding it.[11] Using the model, they showed that this single cell was capable of producing abnormal bursts of action potentials, as may be seen during seizures. The model also illustrated how increased extracellular potassium could lead to depolarization block, during which the cell is depolarized but unable to spike. Some studies have implicated depolarization block in inhibitory interneurons during seizure-like events in brain slices, which could free excitatory cells to spike excessively in bursts.[11, 47]

Then, to examine the role of glia directly, they extended the single cell model to a 200 cell network model consisting of pyramidal and inhibitory cells and accounting for glial function, ion pumps, and diffusion. Their model illustrated how glial dysfunction could cause neural networks to be less resilient to small perturbations such that a network exhibiting normal persistent activity associated with higher level functions could suddenly transition to seizure-like activity.[44] For example, they showed that the rearrangement of astrocytes associated with epileptogenesis leads to increased extracellular potassium concentration and a reduced ability to buffer the extracellular potassium, as well as increased strengths of excitatory synapses.[44] The behavior of their model was consistent with several experimental results,[44] and it underscores the potential of glia as therapeutic targets.

COMPUTER MODELING TO ASSIST RESEARCHERS

Computer modeling and experimentation are complementary in research and the development of therapeutics. Each approach provides unique benefits and is improved by contributions of the other. Though definitive confirmation of scientific fact requires experimental results, modeling serves the field by enabling a flexibility and efficiency not always possible in experiments and can help researchers design more focused experiments.[39]

One example of a scenario in which computer modeling allowed researchers to extend their experimental observations occurred during an electrophysiological study of hippocampal mossy cells (see also above) after head injury. These excitatory neurons, located in the dentate hilus, are among the most vulnerable neurons in the entire mammalian brain;[48] factors including strong excitatory inputs, a sustained response to excitatory input, and a high level of spontaneous activity render them particularly susceptible to excitotoxicity.[49] Significant mossy cell loss is observed in human epileptic tissue and in animal models after experimental head trauma.[50–52] However, several lines of evidence suggest that some mossy cells survive trauma[49–50, 52] and that these surviving mossy cells may spread or amplify dentate network hyperexcitability.

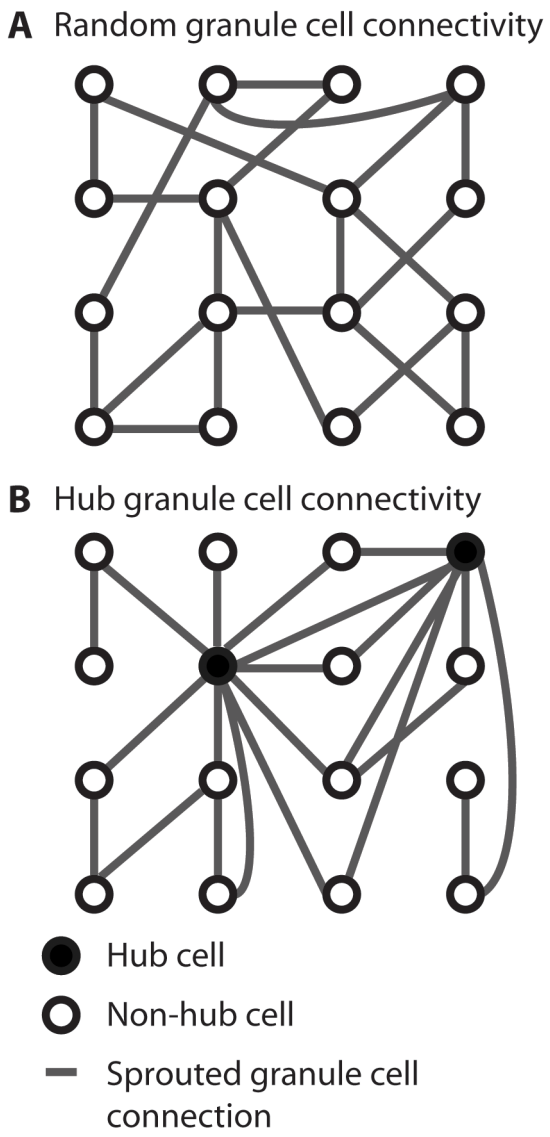

Figure 4. Reconnecting the granule cell network. In temporal lobe epilepsy, granule cells in the dentate gyrus sprout axon collaterals that synapse onto other granule cells, creating a recurrent excitatory circuit. **A:** In the control network, connections were modeled as random, constrained only by the extent of the granule cells' axonal arbors.[17] **B:** In theFPI network model, the same total number of connections are introduced, but the connectivity is different. A few cells are highly connected, while the rest remain sparsely connected. Note that the experimental network depicted here is only a visual guide to understanding the general connectivity of the network.

Howard *et al.* (2007) used a rat fluid percussion injury model to study the changes in surviving mossy cells after head trauma, comparing their *I-F* (current v. spike frequency) and *I-V* (current v. membrane potential) curves before and after trauma.[53] Surprisingly, they found no significant difference. Yet on closer inspection, extensive, opposing alterations were found in various membrane currents and properties that together resulted in the unchanged *I-F* and *I-V* relationships observed in mossy cells after head trauma. The resting membrane potential was depolarized, the tetraethylammonium (TEA)-sensitive potassium current decreased, and the voltage-dependent sodium channel required more depolarized potentials to activate.

Howard et al. then used computer modeling to understand whether each one of these changes would affect the dentate network when considered separately. Notably, when modeled alone, each of these alterations dramatically affected network excitability (Figure 3), despite cancelling each other when occurring together. In this case, the computational model complemented the experimental observations by vividly demonstrating the

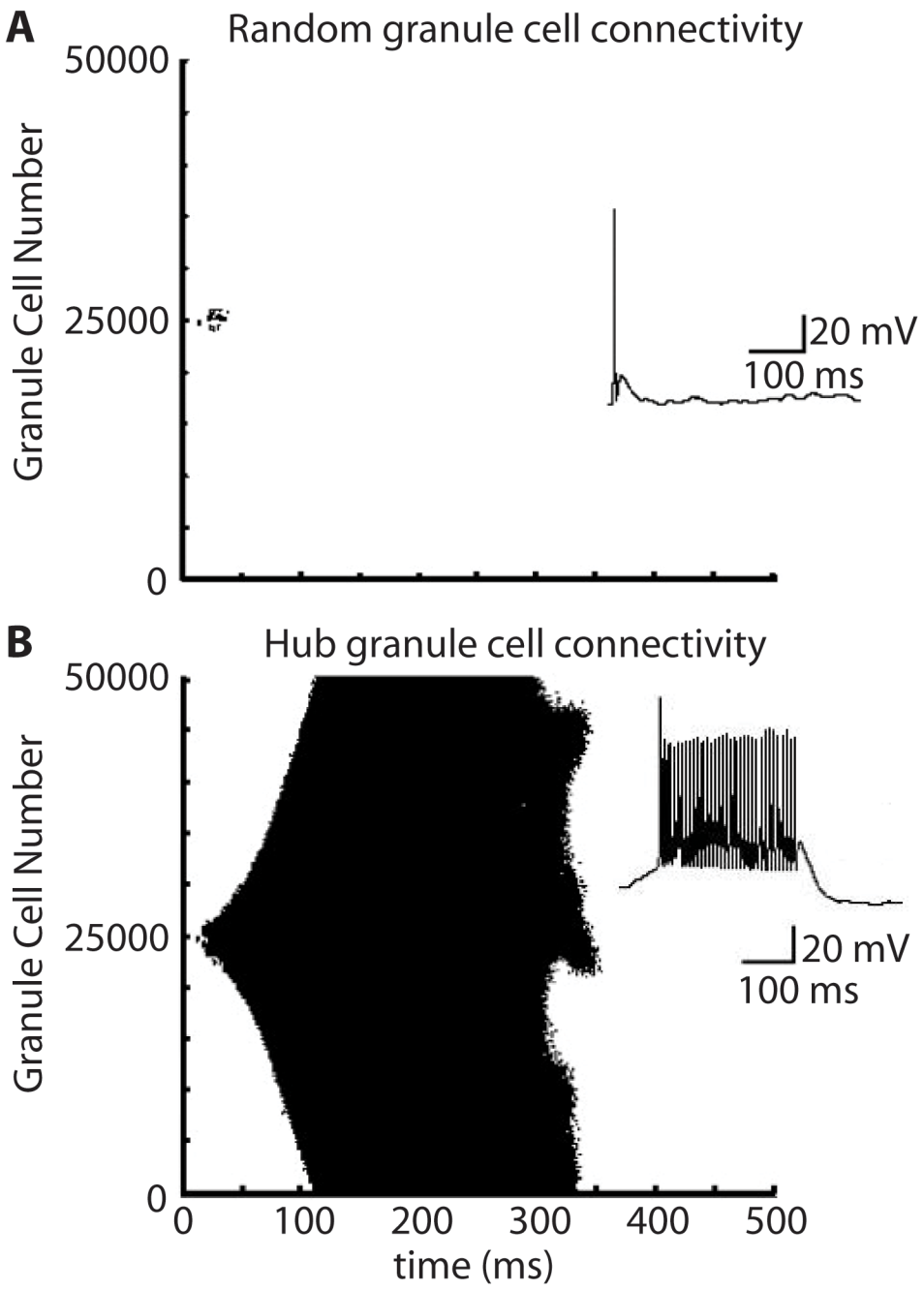

Figure 5. Highly interconnected granule cell hubs greatly augment network excitability. Both A and B represent raster plots of granule cell firing in a network with 50% of maximal granule cell-to-granule cell connections, where stimulation was delivered via the perforant path to 1% of the granule cells. Both networks have the same number of added connections, just distributed differently. Representative firing patterns of cells in the network are shown on the right of the raster plots. **A**: The sprouted connections are randomly distributed throughout the network. **B**: The sprouted connections are distributed such that 5% of granule cells make 210 more connections than the average granule cell and thus serve as hubs. Figure adapted from Morgan et al. (2008), *PNAS*, used with permission; copyright (2008), National Academy of Sciences, U.S.A.[18]

importance of potentially homeostatic mechanisms[54] in regulating overall levels of neuronal activity in large networks.

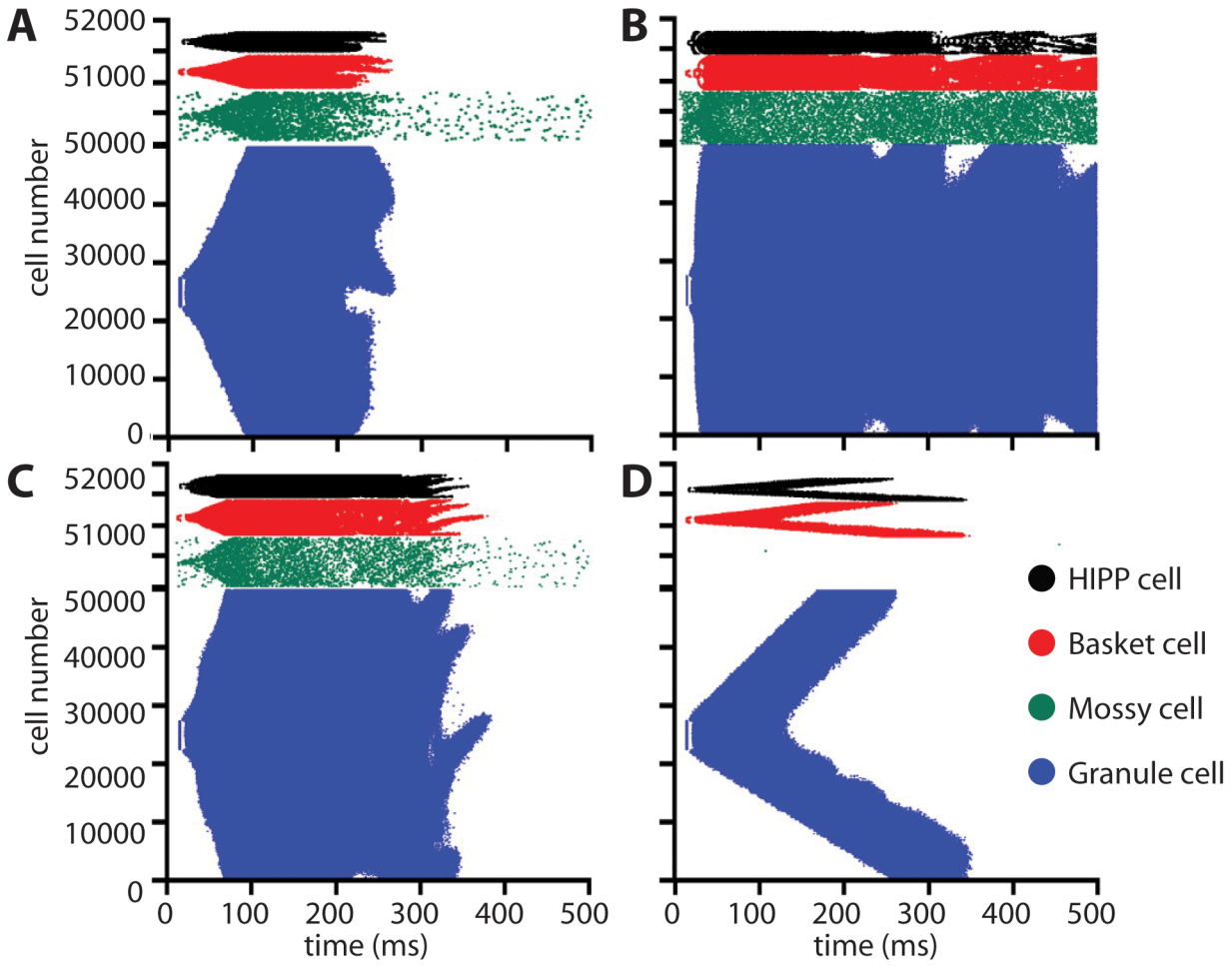

Figure 3. Individual post-traumatic changes to intrinsic properties of mossy cells have robust effects on dentate gyrus network hyperexcitability. Dentate gyrus network activity in response to a single simulated perforant path stimulation at $t = 5$ ms is plotted as cell number versus time. Each single dot represents an action potential in one cell (blue: granule cell; green: mossy cell; red: basket cell; black: hilar-perforant path associated (HIPP) cell). Note that the scale for granule cell numbers is smaller than that for other cells. **A:** Network activity of the dentate gyrus in the fluid percussion injury (FPI) model with biologically realistic levels of mossy fiber sprouting and hilar cell loss. All subsequent simulations were performed with these anatomical changes in place. **B:** Network hyperexcitability is increased when mossy cell V_m is depolarized by 3 mV in the FPI model. **C:** Hyperexcitability of the network is also increased when the model is implemented with an increased mossy cell-to-granule cell synaptic conductance, representing the effect of the increased mossy cell action potential width due to change in tetraethylammonium (TEA)-sensitive potassium current. **D:** Network hyperexcitability is decreased significantly when the activation curve of I_{Na} in mossy cells is shifted by 5 mV. Note that only 2 of the 750 mossy cells fire during the 500 ms simulation. Figure adapted from Howard, et al. (2007), *Journal of Neurophysiology*, Am. Physiol. Soc., used with permission.[53]

SUMMARY OF APPROACHES TO MODELING EPILEPSY

The models described above vary in their level of detail and scope (see Figure 1) and there are valid reasons for the different approaches. Researchers seeking an overall description of seizure dynamics would not necessarily want it to be in terms of the activity of thousands of neurons. For them a higher level approach, based on the assumption that the neural network can be characterized in aggregate terms, would be more appropriate. These aggregate, macroscopic models, such as the Lopour et al. model described above,[14] are often called mean-field models (Figure 1A), indicating that their base components are entire populations of neurons similar enough to be grouped together and described in terms of average properties. Most such approaches are based on a computational model developed by Wilson and Cowan[55] that had two interconnected neuronal populations, one excitatory and one inhibitory. Though the cells are described as populations, using an average, rather than

individually, the average properties are still informed by physiological data. The models often produce results in the form of EEG traces, directly comparable to patient data.

Such models may also make predictions about the role of a cell population in seizure dynamics, such as one model that split the inhibitory population into separate fast and slow components while maintaining a single excitatory population.[13] The model was fit to real patient EEG data taken from pre-ictal, pre-onset, and ictal time periods, and it could produce realistic EEG waveforms. The model made several experimentally verifiable predictions about the role of excitatory and inhibitory populations in seizures, including – paradoxically – that slow inhibition increases prior to seizure onset, but contributes to overall excitation by inhibiting mainly the fast inhibition component.[13]

These macroscopic models have an advantage for describing seizure dynamics because they require relatively few computational resources. Their smaller computational requirements enable them to simulate the longer time periods required to model transitions into and out of the seizure state. Understanding what prompts the transition from non-epileptiform activity to the seizure state is crucial for seizure detection and intervention, and high level models are well suited to describe such system level dynamics.[56]

In contrast, there are questions that call for much lower level, detailed computational models. For example, researchers interested in how a particular ion channel mutation affects network hyperexcitability would need a highly detailed, biologically realistic model that could incorporate well-characterized ion channel properties and output precise spike times for each cell in the network (Figure 1B). Such computational models are also useful for exploring the altered connectivity and cell loss seen in most models of epilepsy.[19] The various models from the Soltesz lab described above are examples of large scale, highly detailed, biologically realistic network models.[17–19, 38, 53]

Even within network models that include multiple, distinct cells, there are a wide variety of approaches. Neurons can be modeled at various levels of detail, ranging from morphologically detailed models with over a thousand compartments or morphologically simplified cells with detailed subcellular mechanisms (Figure 1D) to integrate-and-fire neurons (Figure 1C) and even simpler representations.[34] The level of sophistication at which a neuron should be modeled depends on the complexity of the computation it is expected to perform. While integrate-and-fire neurons may be sufficient to produce expected spiking patterns in some cases,[19] specific distributions of ion channels and synapses along dendrites may be necessary to model more complicated functions performed by neurons, such as coincidence detection.[34] The Cressman et al. models described above[11, 44] employed mathematical neurons with subcellular and extracellular mechanisms described by a few equations. This level of detail was sufficient to answer the questions they posed in the model, and enabled them to run the longer simulations necessary to characterize the dynamics in the ion concentrations. To model the astrocytic rearrangement more concretely, as they propose for future work, a more detailed model that incorporated 3D cell positions would probably be necessary.[44]

As mentioned in passing above, computer modeling is limited by time and resource availability. If a model contains very detailed components (such as numerous ion channel types or detailed cell morphology), it may be necessary to remove complexity from another area of the model, either the scope (number of cells) or the length of simulation time (whether the model simulates activity occurring over a few milliseconds or several days). For this reason, often the more detailed a model is, the smaller its scope and simulation time.

Because of the above limits, computational models used in epilepsy generally describe only part of the disorder,[20] such as aggregate electrical dynamics during seizures[13] or altered neural connectivity found in the affected areas of the epileptic brain.[19] While partial models can provide much insight, there is significantly more explanatory power in a model that answers questions covering multiple levels simultaneously, such as: “how do the altered firing patterns of cell type ‘A’ influence the EEG signal after seizure onset?”

THE FUTURE OF COMPUTER MODELING OF EPILEPSY

Given the rapid rate at which technology is developed, it is easy to imagine that computers will soon be fast enough to support a detailed, biologically realistic model of the entire human brain that could answer questions such as the one above.[5] Today modelers must pick between modeling seizure dynamics and transitions (which require lengthy simulation times) or detailed biological structures and mechanisms; in the future it will be possible to do both at once. Such a powerful model would represent a significant tool for understanding overall seizure and transition dynamics in terms of network and cell-level activity, an area of epilepsy research that needs significant development.[47]

Already, advances in neural simulation tools allow them to run simulations in parallel (on multiple computers at once) in a fraction of the time it would take to run the same simulation on a single processor. These parallel models can support far more neurons and detail so that, for example, network models focusing on altered connectivity in epilepsy can be scaled up to full size to enable more realistic neural connectivity. Additionally, detailed network models of particular brain regions could be made bilateral. Both computational models and *in vitro* experiments generally approach epilepsy "unilaterally," without regard to which side of the brain is being observed or any effects of the contralateral hemisphere. However, the two sides of the brain vary remarkably in ways relevant to epilepsy. For example, there is known to be significant asymmetry between the bilateral connections of the hippocampal formation.[57] Bilateral models could address the effects of contralateral connections and asymmetry[57] on seizures and seizure generalization.

The computational models all described so far have been simulations, in which software is configured to produce the model. However, as we create models with increasing numbers of cells, it is worth noting that a model of the whole human brain would be quite resource-intensive. For example, the Blue Brain project mentioned above uses 8,192 processors to model 10,000 highly detailed, multi-compartmental neurons with 100 million synapses.[5, 58] A model of the whole human brain would need to include 100 billion neurons and 10 quadrillion synapses, an expensive endeavor that is projected to require millions of processors and roughly 100 megawatts of power.[58]

To overcome these limitations, another approach toward modeling has been developed. Rather than configure software, some modelers are configuring hardware to emulate neural networks, such as the recent Neurogrid project.[58] The resulting neuromorphic chips can be combined to produce a device capable of emulating a million neurons and six billion synapses in real time. Though these neurons are less detailed than those on the Blue Brain computer, they still contain multiple compartments and realistic ion channels. Highly detailed neurons can be modeled as well if the overall number of neurons is decreased; models with hundreds of compartments and any number of distinct ion channel types are not unfeasible.[58]

One of the main arguments against hardware modeling is its lack of flexibility. However, significant improvements have been made against this limitation. The current Neurogrid device can support 16 different cell types, with each type having its own combination of ion channels.[58] The connections between cells are programmed using random access memory (RAM) and can be changed on demand. The results of the neuromorphic simulations can be viewed on an interactive display in real time at various levels, from the spike patterns of a single cell to the activity of a whole cortical layer. The applications of such a tool to epilepsy research are apparent: the ability to quickly model such a large number of neurons over a large simulation time is just what we need to characterize seizure dynamics in terms of cell and ion channel activity.

COMPUTER MODELING RESOURCES

Computer modeling is a useful research tool available to almost everyone. The monetary investment in computer modeling can be small, requiring resources available to anyone with a computer and internet access or,

for more intensive modeling, resources readily accessible at research institutions or through multipurpose shared resources such as the National Science Foundation's TeraGrid.[59]

Researchers and clinicians interested in computer modeling are urged to explore the many computational models freely available online at the ModelDB website.[60] In most cases, the software used to create such models are also freely available online (e.g. the neural simulators NEURON[61] and GENESIS[62]) or through network licenses at academic institutions (MATLAB[63]). The time required to learn these programs is comparable to the time required to learn various experimental techniques and results can be obtained quickly. Importantly, the researcher has far more control over the factors important to obtaining results from models than is possible with experiments.

The large scale, detailed, biologically realistic models referenced above employed NEURON, but many successful models have employed GENESIS as well. For example, van Drongelen et al. (2007) produced a detailed, 656 cell neocortical network with GENESIS.[64] The model included two types of pyramidal cells, basket cells, and chandelier cells, with small world connectivity. The cells contained realistic ion channels and gap junctions. They used this model to explore the effect of synapse weights on the ability of the cortical network to form and sustain seizure-like oscillations and to observe the activity displayed by subpopulations of neurons during these oscillations. Surprisingly, among other results, they found that a weakening of excitatory connections in the neocortex may enable the propagation of seizure-like activity and concluded that strong excitatory connections are not always necessary for a network to produce seizures.[64]

Both NEURON and GENESIS can be run in parallel, which allows for a near linear speed increase in modeling time; to run a model for the same simulation on two processors will take roughly half the time taken to run the model on one processor. The authors recently ran a 1000 ms simulation of over one million detailed cells in under 2 hours, using parallel NEURON on 608 processors.[65] MATLAB can be run in parallel as well, using its Parallel Computing Toolbox.

All three of these software programs have extensive online documentation, tutorials, and user forums supported by the software developers. Both NEURON and MATLAB regularly hold in-person workshops as well. While both NEURON and GENESIS have graphical user interfaces (GUIs), these GUIs are generally most useful when building single cell models. For network models, there is a simulation software-independent tool called NeuroConstruct, which provides an interface to NEURON, GENESIS, and other programs for those who prefer not to work with code directly.[66]

In addition to software-specific resources, there are some excellent books on computational neuroscience in general[67] and computational modeling of epilepsy in particular,[9] useful for the potential modeler or anyone wanting a deeper understanding of computer modeling in neuroscience and epilepsy.

CONCLUSION

A detailed model of the entire human brain, which could be accessed at any level of detail and be personalized for individualized patient treatment analysis no longer looks quite so outlandish. Likewise, it appears that an implantable seizure detection and intervention device will be available as a standard treatment option before long. Such exciting advancements made possible through computer modeling should inspire researchers and clinicians to be even more creative in their approaches to epilepsy therapies. We look forward to the advances the next decade will bring in computer modeling of epilepsy.

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